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18407

Distr.
LIMITED

ID/WG.502/6(SPEC.)
25 May 1990

ORIGINAL: ENGLISH

United Nations Industrial Development Organization

Interregional Meeting on Co-operation among Developing Countries for the Development of the Pharmaceutical Industry

New Delhi, India, 19-22 March 1990

PLANT DERIVED THERAPEUTIC AGENTS

The Indian Experience*

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19

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Table of contents

1. BACKGROUND

The history of the treatment of disease is intimately woven with that of medicinal plants. Some of the more important facts in this regard are given below.

(a) The earliest medicines used by mankind were obtained from plants, as plants were available in the immediate environment. Over the millinia that followed the most effective medicines amongst them were selected by 'trial and error' methodology, and have become a part of the ethnomedical tradition. In many cultures such as India, China and the Arab world this experience got systematically recorded and incorporated into the regular systems of medicine that developed and became a part of the materia-medica of the Traditional Systems of Medicine. A significant proportion of the population, particularly in developing countries [estimates vary from 50-75%] still use these traditional drugs, some because of lack of easy access to drugs of the modern system, but many by deliberate choice on account of their faith in them.

(b) The modern drug research in Europe started in the last century with analysing plant drugs. A number of drugs obtained from plants are still largely used in modern medicine (Table 1&2), and form an important segment of the modern pharmacopoeia; no commercially viable synthetic methods are likely to replace the production of many of them from medicinal plants. A number of important chemical intermediates needed for manufacture of drugs are also obtained from plants some of which are also listed in Table 1.

(c) The structures of the active constituents of these plants have been an important source for leads for drug design; many of the modern drugs are based on these leads. The study of medicinal plants, therefore, continues to be an important component of modern drug research to cover and provide novel structural leads. This is of particular importance in search of drugs for diseases for which modern drugs are inadequate, and there is presumptive evidence of efficacy of some medicinal plants. Further there is an undercurrent of disenchantment with modern drugs on account of the side effects observed with them and greater emphasis in their use being on the disease and not the patient. And there is a resurgence of interest in traditional system remedies which had a more holistic approach to therapeutics.

(d) Plants are a renewable source; and with the recent developments in biotechnology the yield of active constituents and cultivation practices of plants can be greatly upgraded.

In view of this wide-ranging importance of medicinal plants, an integrated developmental approach is required to fully exploit the potential of this resource in medicare programmes and to provide this sector a proper scientific, economic and industrial base.

2. RESEARCH AND DEVELOPMENT FOR THE UTILISATION OF MEDICINAL PLANTS FOR THERAPEUTIC USE

2.1 Traditional System Remedies:

The traditional system remedies, inspite of their ancient origins, are of great relevance even today on account of their widespread use in many countries, several factors are attributable to this[1,2]. This important resource for therapeutic agents must be fully used in order to be able to provide a medical service for the whole population. Many R&D inputs would, however, be needed for this; some suggestions for this are given below:-

i) Determining the place of these medicaments in national medicare programmes in the light of contemporary developments in therapeutics.

ii) Investigating them for development of new drugs, particularly for conditions for which suitable drugs are not available.

iii) Validating the claims of traditional drugs using modern tools and methods.

iv) Developing quality control standards and updating the technology for the production of traditional drugs.

2.1.1 Place of traditional medicaments in national medicare programmes: Drugs, irrespective of the source from which they are derived, are a means to relieve suffering and maintain good health; the objective is to provide drugs at an affordable cost to the entire population of the country. It is, therefore, important to delineate the areas or the diseases for which modern drugs are more suitable and are needed and areas where drugs of traditional systems can provide medical relief and shoul be used. All drugs, from whatever system they are obtained should be integrated into one comprehensive national system of health care. A group of physicians and pharmacologists should be given this responsibility.

2.1.2 Development of new drugs: There are a number of conditions for which suitable drugs are not available in the modern system of medicine and where the traditional system have the possibility of offering new drugs; some such conditions are indicated below where new drugs are urgently needed. The possibility of finding new drugs is much greater if the choice of traditional remedy/medicinal plant to be investigated is based on its specific mention in traditional system texts.

1. Tropical diseases
   - 1.1 Antimalarials
     - Tissue schizontocides
     - For multidrug resistant blood schizontocides
   - 1.2 Antifilarials
2. Antirheumatics

3. Immunomodulators
   - As adjuncts for chemotherapy
   - Adaptogens
4. Antivirals
5. Hepatoprotectors
6. Would healing agents
7. Mental deficiency & Memory
   - Alzheimer's disease
   - memory enhancers

The area of immuno-modulators and hepatoprotectors is of particular relevance in the context of traditional systems of medicine, as there is much emphasis on promotive health (Rasayana) in Ayurveda, and proper functioning of liver in these systems, and certainly modern drugs are inadequate in these areas. Traditional system remedies should be specially investigated for treatment of such diseases.

2.1.3 Validating the claims of traditional drugs using modern tools and methods:

It is certain that the traditional system drugs have been used for millennium of years. Therefore the sanction of the use for long periods is on their side. But to be of use on scientific basis and also to establish their position vis-a-vis modern drugs that are available from other systems, it may be more important to validate the claims of traditional drugs using modern tools and methods for which the following suggestions are made:

i) Routine animal models may not be adequate in many situations
ii) Minimal toxicology studies
iii) Clinical trials; Phase I, II & III
iv) First testing of drugs in the manner they are used in traditional medicine.
v) Special emphasis on pharmaceutical forms
vi) Undue emphasis on pure compounds is unnecessary; standardised fractions could also be used and in some cases may even be better.

2.1.4 Develop quality control standards and updating the technology of traditional drugs: In view of the usage of the drugs of the traditional systems it is important to update the technology for their production. One of the most serious drawbacks with the traditional system of drugs is that there are no standard methods for their quality control criteria. Therefore, it is not possible to ensure reprocessing of the drugs from batch to batch. One factor which is often considered to stand against standardisation of these drugs is that these are crude extracts and are mixtures of a number of plants. However, modern instrumentation and biological assay methods do provide the possibility of developing suitable quality control criteria even on mixtures. It is, therefore, suggested that if we have to make fuller use of the drugs

of the traditonal systems, we must do the following:-

(i) Develop quality control standards using:
   a) IR, UV, GLC, HPLC fingerprints
   b) Chemical assay based on percentage content of one or two important pharmacologically active chemical constituents
   c) Bioassay methods

(ii) Simplify and modernise methods of preparation

(iii) Determine the pharmacokinetic and bioavailability parameters, wherever possible and necessary.

2.2 Broad spectrum biological screening of plants

The number of plants used for preparing traditional remedies in various countries and those that have so far been investigated scientifically constitute only a small fraction of the plant resources of the world; large proportions of the plant growing in developing countries have not been investigated; it is estimated that only about 5000 of the 30,000 plant species available have so far been adequately investigated. Moreover, even in the case of plants that have been screened in one continent one has to bear in mind the well-known possibility of variation in the chemical composition of the same plant growing in different geographical and climatic regions. It is, therefore, necessary for every country to undertake systematic biological screening of all the available plants from different climatic zones. It must be emphasized that the collection, storage and processing of plants must be done in such a manner that their chemical constituents are not affected. Bioassays, in vitro and in vivo have to be developed which can measure even weak activities due to minor constituents. The biological test systems employed should be particularly directed to the therapeutic conditions for which satisfactory drugs are not so far available. Here it should be pointed out that the above approach is quite different from the classical phytochemical investigation of medicinal plants. The latter concentrates primarily on isolation of pure chemical constituents, their characterisation and structural elucidation, and the testing for biological activity of pure constituents is only subsidiary. In contrast, the former approach involves monitoring for biological activity at every step of chemical fractionation/purification. The active plant constituents thus characterised, may not always possess the most acceptable pharmacological toxicological profile, but could serve as leads for manipulative synthesis resulting in useful modern therapeutic agents. Screening of plants has infact, provided many novel structural leads in the history of drug research and continues to do so. Plants are a reservoir of potentially useful chemical compounds to serve as drugs or useful leads for drug design by synthesis[3,4].

2.3 Cultivation of medicinal plants

The availability of adequate quantity of the required medicinal plants is very often a limiting factor for the success of the phytochemical industry. Connected

with availability is also the question of the genetic improvement of the species in terms of yield of the active constituents or the selective improvement in yield of the required constituent; digitalis plants have been selected which give mainly digoxin or digitoxin; similarly in ergot strains have been developed which yield mainly ergotamine or ergometrine; and the success of the industry based on medicinal plants has depended very largely on the development and propagation of these special varieties of plants. The recent developments in clonal micropropagation of plants through tissue culture techniques has greatly helped in this area. Some of the medicinal plants which have been successfully cultivated through tissue culture technique are Cephalis Ipecacuanha[4], Rauwolfia serpentina[5], Disscorea sp.[6], Valerian[7], Hyocyamus niger[8], Dubosia sp.[9], Solanum sp.[10,11], and Cinchona[12]. Recent advances in plant genetic recombination techniques have added a new dimension to the possibilities of plant variety improvement and has become a priority area for R&D. Attention should, therefore, be given to the R&D for the cultivation and genetic improvement of medicinal plants. The number of medicinal plants of well established economic value required in large quantity is around 50, and first attention should be given to the cultivation of these plants[13]. There is also a great potential for export of medicinal plants.

Economic mapping: Connected with this is the desirability of collecting information on the natural availability of selected plants through economic mapping, which provides useful information while planning for collection. This will also provide information about the availability of original germ plasm, which needs to be preserved.

The main thrust in R&D in this area should be given to the following:-

- economic mapping for important medicinal plants
- preservation of germ plasm
- improvement of varieties
  - * classical selection method
  - * genetic recombination techniques
  - * Clonal propagation
- introduction of new varieties by classical or tissue culture method
- standardisation of post-harvest technology for preservation and transport of plants.

2.3.1 Plant cell culture for production of pharmaceuticals: Connected to tissue culture is the area of plant cell culture, which in principle is very appealing. While a number of medicinal products have been produced in the laboratory, in experimental fermenters, industrial production has so far been successfully achieved with only a few products. But there is need to undertake R&D in this area as it offers great possibilities for industrial production[14].

2.4 Phytochemical Industry

Drugs derived from plants continue to be largely used in health care, both in modern medicine and in traditional systems. In modern medicine these are mainly

used as pure substances and some as standardised extracts or tinctures; table 1 lists some of the important pure plant products and Table 2 standardised extracts that are currently in therapeutic use in modern medicine. Most of the traditional medicines are used as crude drug powder, decoction or extract of single or mixture of plants. The technology, machinery and equipment required for the production of most of these plant products is relatively simple most of the developing could profitably set up manufacturing plants for the production of these products, which will help both in health care and economic improvement. Depending upon the technological status first the production of standardised extracts could be taken up and going onto pure compounds; there is a market, for both extracts and pure products; the isolation of pure constituents would of course provide much more added value and wherever possible should be carried out. In the case of traditional systems remedies it would be useful to modernise their production develop appropriate formulations and dosage forms and quality control standards.

The advantages of setting up local industry[1] for providing more employment import substitution and health care are quite well known.

One of the essential prerequisite for the starting of this industry is the availability of the plant species; an industry can not be built on spontaneously growing plants for reasons of species depletion and variability of quality; cultivation on a cropwise basis must be organised. The R&D needed for cultivation of plants is described in point 2.3. Simultaneously process technology studies should be carried to optimise the production of the specific chemical constituents (or plant extracts), and transferred to a pilot plant scale, and then to a commercial scale.

Management and marketing is another aspect to which adequate attention should be given. The medicinal plants industry should thus be concerned with:

- modernisation of the production of traditional system remedies in factories, with standardisation of quality
- production of plant drugs of established economic value of new formulation/ dosage forms based on traditional remedies, and their adoption in modern medicine.

2.5 Regional Medicinal Plants Research Centre

The setting up and running of the medicinal plants industry would be greatly helped by constant inputs of modern technology in isolation, and separation techniques and development and production of formulations from the products thus obtained. A certain amount of this R&D could be and should be carried out by the industry in-house, but this work could bemore effectively carried out at a research centre soleiy devoted to R&D. In view of the high capital and recurring cost involved in

R&D, this is an area in which there could be active collaboration among developing countries. Starting with development of technology, this centre should gradually also undertake research in the development of new products and new drugs from medicinal plants. No doubt drug research requires a multidisciplinary team (consisting of organic chemists, pharmacologists, biochemists, chemical technologists, pharmaceutical scientists, toxicologists, clinical pharmacologists and clinician, working together) and has become highly cost and time intensive on account of stringent drug regulatory requirements; on an average the development of one new drugs whether synthetic or obtained from plants, costs US $ 50-75 million and a time of 10-12 years but with proper priorities in research it could serve a useful purpose. Not many developing countries have well trained scientists in all the disciplines mentioned above, or the resources to undertake research to develop new drug. But the priorities for new drugs of developed and developing countries are very different, and developing countries have to develop drugs for their needs on their own. The only way to solve this problem would be by fostering active collaboration among developing countries of a region, by establishing Regional Research Institute. To begin with an existing laboratory having the core facilities could be identified and a nucleus of this centre created in this laboratory with scientists from different member countries working together. As the work progresses this centre could plan to have a building of its own and become a separate full fledged Institute.

The main objective of this centre would be to:

(a) promote the industrial utilisation of the medicinal plants of the region

(b) develop new drugs from the medicinal plants of the region for diseases of particular relevance to the region

(c) survey the plant resources of the region

This Institute should have the following scientific divisions:

1. Phytochemistry Division
2. Process Development Division
3. Pilot Plant & Project Engineering
4. Microbiology Division
5. Pharmacology Division
6. Pharmaceutics Division
7. Economic Botany Division
8. Toxicology Division
9. Clinical Pharmacology Division

3. THE INDIAN EXPERIENCE

3.1 Practice of Ayurvedic medicine today

Currently there are around 250,000 (April, 1986) registered medical practitioners of the Ayurvedic system (total of all traditional systems around 291,000) as compared to about 700,000 of the modern system; in every State in India about 1/3 of the government medical posts are occupied by physicians belonging to the traditional systems.

Training of students has been an essential part of the Ayurveda tradition. There are records of organised/regular training programmes for medical practitioners in the old Universities such as that of Taxila from 500 B.C. onwards. Much of the training of course was also imported by tradition and heritage. At present, there is organised teaching and training in India for traditional systems more or less on the same pattern as for the modern allopathic system.

The extent of drug usage is hard to quantify for traditional systems as by tradition most of the practitioners manufacture and formulate their own prescriptions; though now there are about ten centralised traditional system drug manufactures whose individual annual production is over $ 10 million whilst the largest one has an annual production of about $ 112 million (June 1988). Their total present annual turnover would be about $ 250 million (as compared to $ 2320 million of modern drugs in 1987). The production by these large manufacturers, though carried out according to traditional prescriptions, is mechanised and automated, and conforms to the normal GMP practices. The drugs marketed include both generic drugs and some branded products. In addition many of the modern drug companies do market a few branded Ayurvedic products.

In 1959 the Government of India decided to recognise the various Traditional Systems of Medicine as distinct entities. Since 1964, and as modified in 1982, the Drugs & Cosmetics Act of the Government of India has included special provisions on Traditional systems drugs. Each drug of the traditional systems has also got to be licenced and registered with the State Drug Control Authority. If any new drug to be introduced is manufactured strictly according to traditional systems materia medica, the Drug Controller need not insist on safety and clinical trial data. There is a separate book of standards for Ayurvedic formulations. All the Indian States are empowered to appoint independent Drug Controllers for traditional systems. In practice, however, in most Indian states the Drug Controller is common for all the systems of medicines. At the federal government level also the Drug Advisory Board and the Drug Consultation Committee is common for all systems of medicine. An Ayurvedic Medicine Pharmacopoeia is available. A Central Pharmacopoeial Laboratory of Indian Medicine has been established to monitor drug standards of Ayurvedic, Siddha and Unani system drugs. As most of the drugs are mixture of plants, standardisation is a difficult job, but one that has to be done. The Central Government has three separate councils, one each for Ayurveda, (including Siddha), Unani and Homeopathy, to advise on all matters pertaining to the practice of these systems of medicine.

It is estimated that a total of about 1000 Ayurvedic remedies are used at present, prepared from some 750 plants; about 430 remedies are included in the Ayurvedic Pharmacopoeia brought out by the Indian government. The Central Council for Research in Indian Medicine and Homeopathy, has published a compendium of commonly used Ayurvedic remedies.

3.2 Research on Plant Drugs

In view of the extensive use of plant-derived remedies, they have been the subject of much research in India, both to make better use of these remedies and to use them as resource material. The general research approaches includes the selection of medicinal plants, preparation of crude extracts biological screening and detailed chemico-pharmacological investigations, identification of active products and fractions, preclinical toxicological and clinical trials, standardisation and use of these active agent molecules as the lead molecules for drug design.

With a view to verify scientifically the claims of the traditional systems of medicine, and to develop new drugs which would be acceptable to modern medicine, two distinct approaches have been followed: first, direct clinical trials of the more commonly used traditional remedies followed by chemical and pharmacological studies and second, broad-spectrum screening of individual plants, both those mentioned in the traditional systems of medicine and others, followed by chemical, pharmacological, pre-clinical and clinical drug-development studies. Prof. R.N. Chopra, a pharmacologist School of Tropical Medicine in Calcutta, was a pioneer in research in plants used in the traditional system of medicine, and carried out extensive studies in this area but with emphasis on pharmacological studies.

Another pioneering investigator was the chemist, Dr. S. Siddiqui, whose work on Rauwolfia serpentina in the 1930s led to the isolation of the well-known drugs, ajmaline and ajmalicine (these names for alkaloids were given after the great Unani physician in India, Hakim Ajmal Khan, who had suggested this plant to Dr. Siddiqui for investigation). Siddiqui had also isolated reserpine but since there was no close collaboration between chemists and pharmacologists/clinicians, its biological activity was not uncovered. A large amount of chemical investigation of medicinal plants was carried out during this period in University Chemical Laboratories, but these products were either not biologically tested or poorly tested.

In view of the great importance that Indian Government after independence attatched to this work established the Central Drug Research Institute, Lucknow, in 1951 with the major charter to carry out an integrated programme of coordinated chemical and biological studies on medicinal plants. Some of other CSIR Laboratories such as Regional Research Laboratory, Jammu, Indian Institute of Chemical Biology, Calcutta and some laboratories of the Private Industry, such as Hoechst Research Centre, also carry out these integrated studies on Indian medicinal plants.

3.2.1 Cultivation of Medicinal Plants: Medicinal plants required by the industry are either collected from the wild or cultivated; some are indigenous, while many

others have beer introduced from abroad. The introduction has required large inputs of research, for example to standardize and improve agronomic practices, to select and improve genetically the varieties to obtain specific plant constituents. A number of research laboratories in the country have been involved in this exercise and have made significant contributions. To focus attention in this area and to have a nodal laboratory for the purpose, the Central Institute of Medicinal and Aromatic Plants (CIMAP) has been established at Lucknow. Its objectives are the introduction improvement and cultivation of medicinal and aromatic plants. A number of private-sector industries are also now active in this area and have established their own farms. Cultivation of plants is carried out by small farmers who are supplied planting material by either a government laboratory or industry; the latter usually purchase the crop from the farmers for processing, thus 'offtake' of their crop is assured.

India is also set to exploit the emerging plant tissue culture based on innovative genetic engineering technique. Industrial houses, agricultural research institutes, national labs. and private commercial groups are all making determined efforts to exploit the potentials of tissue culture.

3.2.2 Ayurvedic Drugs: There has been considerable research on Ayurvedic drugs both to put their usage on a modern scientific footing and also to obtain leads for the development of drugs for the modern system.

With the compilation of the Ayurvedic Pharmacopoeia attention has been focussed on the need to ensure standards of quality and reproducibility in products. Most of the Ayurvedic drugs are a mixture of a number of ingredients, which no doubt present difficulty in quality control assay by conventional methods. However, the sophisticated spectroscopic and separation methods and the bioassay methods, both *in vitro* and *in vivo*, now available offer the possibility of developing suitable quality control criteria for these preparations. Further, the safety of these drugs cannot be taken for granted merely because these have the sanction of centuries of use. It is necessary to confirm their safety by toxicity studies. This will help in making traditional system remedies more acceptable in modern therapeutics. Clinical trials, particularly of drugs used for acute life-threatening situations, may also be necessary to place these drugs vis-a-vis the modern drugs in the correct community health perspective.

Traditional system drugs have been the starting point for the discovery of many important modern drugs. This fact has led to chemical and pharmacological investigations of these plants and to the undertaking of general biological screening programmes of plants not only in India but all over the world. Some of the contributions of Ayurveda on this count are discussed later. Much of the work under these programmes

has been centered round individual plants, and often the emphasis has been on chemical investigation. It is necessary to first test the products as they are used in traditional medicine, and if the desired activity is confirmed to then investigate individual plants, before going onto active fractions and pure constituents of each plant. Further, while general screening programmes have their own place to help identify new and unexpected leads, the chances of finding activity are greater if drugs are tested for the activities already described in the classical texts; one such example is that of gugulipid as a hypolipidaemic agent[1,15]. Broad biological screening of plants and specific testing for an activity for which the drug is valued in Ayurvedic texts are thus complementary approaches to new drug development and are not mutually exclusive.

A question which is often asked is what are the areas in which Ayurvedic drugs are of special value. There are some diseases for which there is need for new drugs as the modern system has either no or only inadequate drugs, while Ayurveda, because of its special traits, does seem to offer some remedies which could be fruitful areas of investigation. One such area is that of hepatoprotectors. The drugs available in the modern system of medicine for providing protection against these disorders are most inadequate and at best provide only symptomatic relief. However, in the traditional systems of medicine of many countries a number of herbal drugs are claimed to provide protection against hepatitis and are widely used as cholagogues/choleretics. In India, based on Ayurvedic texts over 30 proprietary products are marketed for liver disorders; these represent a variety of combinations of about 50 plants. Many of these preparations are widely used by modern physicians as well. Extracts of a number of these plants have been tested individually both in different experimental models of liver disorder, and in a few cases clinically and some have shown promising activity, Picrorrhiza kurroa is one such plant[16].

There is thus significant presumptive evidence for the efficacy of a number of Ayurvedic drugs for liver disorders. In some cases where safety is assured direct clinical trials may be in order to evaluate their efficacy. Although many individual plant constituents have been tested and found to exhibit activity in different experimental models, more comprehensive SAR studies are needed to understand the different pathological situations in which different classes of compounds act. Some new experimental models may also have to be developed for these studies.

Other areas in which Ayurveda offers prospects of finding useful drugs are wound healing, immunomodulation, arthritic conditions and urolithiasis where modern drugs are inadequate, and it would be useful to investigate these drugs. The use of metal preparations including gold, mercury, iron and zinc in Ayurveda (including in Siddha) for a variety of disease conditions and as tonics is also noteworthy andmay have some leads to offer.

The chemo-pharmacological investigation of medicinal plants of traditional systems has also resulted in the discovery of some new drugs for the modern system[17], which include Ajmaline and Ajmalicine from R. serpentina for CNS disorders, psoralens from Psoralea corylifolia for leucoderma and Commiphora mukul resin steroids as hypolipidaemic agent.

3.2.3 Broad spectrum biological screening: The CDRI apart from studying medicinal plants and drugs of the traditional systems of medicines has also initiated a systematic broad spectrum biological screening programme of Indian plants, irrespective of whether these plants are used in traditional system drugs or not. Over the last 2 decades over 3000 plants have so far been collected and screened, and many plants have shown promising activity[18]. Such screening programme have also been carried out by Hoechst Research Centre, Bombay and former Ciba-Geigy Research Centre, Bombay. Interesting biological activity hjas been identified in a number of plants as a result of this screening one of most interesting out come of this screening has been the demonstration of hypotensive, cardiotonic, adenylate cyclase stimulating and platelet aggregation inhibiting activity in a diterpene obtained from Coleus forskohlii[19,20].

3.3 Medicinal Plant Industry

Plants are the only economic source of a number of well-established and important drugs; in addition, they are the source of some chemical intermediate needed for the production of many others. At a rough estimate, 25 per cent modern drugs are directly or indirectly derived from plant products.

Before independence, the production of plantbased drugs in India was confined mainly to cinchona and opium alkaloids in three stateowned factories; the other products were mainly galenicals (i.e. extracted from plants) and tinctures. In the last three decades, bulk production of plant drugs has become an important aspect of the Indian pharmaceutical industry. Some of the drugs which are manufactured today are listed in Table 1; many of them are also exported. Drugs for which technology has been developed andthe production is likely to be undertaken in the near future include L-dopa from mucuna beans. India has thus since independence moved on from export of crude drugs through total extracts to production of bulk drugs, steroid intermediates.

In India today there is a sizeable-steroid industry based mainly on raw materials obtained from plants, particularly diosgenin. Earlier, the only economic sources of diosgenin were Discorea deltoidea and D. prazeri which grow wild in the mountains, but this source is being depleted because of indiscriminate uprootings and slow growth of the tubers. In recent years, a major breakthrough has been the successful cultivation

of D. floribunda, D. composita and other hybrid varieties in the plains of many regions in the contry. A number of of units have now been established for the production of diosgenin, and the steroid industry seems well set towards growth. A number of pharmaceutical companies now make 16-dehydropregnenonolone acetate (16-DPA) and dehydroepiandrosterone (DHA), which are important intermediat s for the production of sex hormones, contraceptive steroids and corticosteroids; a significant quantity of these derivatives is exported.

Beta-ionone, obtained from lemon-grass oil, is yet another intermediate of industrial importance and is used for the production of vitamin A.

4. CONCLUSIONS AND RECOMMENDATIONS

Medicinal plants continue to provide valuable therapeutic agents, both in modern medicine and in traditional systems. Medicinal plants also offer good prospects of finding new drugs particularly against conditions for which modern drugs are in adequate. Medicinal plant industry manufacturing these therapeutic agents will greatly helpthe health care programme and also add to economic improvement of the developing countries. Medicinal plants industry should undertake to:

(a) Cultivate medicinal plants needed for processing, including their genetic improvement;

(b) Modernise the production of traditional remedies by production in factories, and develop quality control standards for them; promote greater use of these standardised remedies in health-care programmes.

(c) Establish phytochemical industry to manufacture standardised plant extracts and or pure medicinal plant products of established economic value for use in modern medicine.

(d) Develop new dosage form based on remedies used in traditional system and promote their adaption in modern medicine.

(e) Carry out R&D for the development of technology for production of medicinal plant products of established value and also to discover new medicinal agents from ethnomedical or traditional remedies; organise systematic broad spectrum biological screening of the flora of the country; foster cooperation between academic institutions and R&D laboratories within each country and of the region; consider setting up a Regional Medicinal Plants Research Centre.

Table 1: Some Phytochemical agents currently employed in modern therapeutics.

Compound	Plant Species
Ajmaline	Rauwolfia serpentina
Ajmalicine	Catharanthus roseus, Rauwolfia spp.
Berberine	Berberis spp.
Caffeine	Camelia sinensis
Codeine	Papaver spp.
Colchicine	Colchicum autumnale/Gloriosa superba
Curcumin	Curcuma longa
Digitoxin, Digoxin, Digitoxigenin	Digitalis lanata, Digitalis lanata
Emetine	Cephaclis ipecacuanha
Eugenol	Cinnamomum spp.
Glycyrrhizin, Glycyrrhizinic acid	Glycyrrhiza glabra
Hyoscyamine	Datura spp.
Hyoscine	Duboisia spp.
Hesperidin	Citrus spp.
Menthol	Mentha spp.
Morphine	Papaver spp.
Papain	Carica papaya
Quinine, Quinidine	Cinchona spp.
Reserpine & deserpidine	Rauwolfia serpentina
Rutin	Cassia spp. Fagopyrum spp.
Santonin	Artimisia cina
Sennosides A&B	Cassia angustifolia, C. acutifolia
Vincaleucoblastine (Vinblastine)	Catharanthus roseus
Vincristine (Leurocristine)	Catharanthus roseus
Xanthotoxin	Ammi majus
Podophyllotoxin	Podophylum emodi
CHEMICAL INTERMEDIATES	
Diosgenin	Dioscorea spp.
Solasodine	Solamum spp.
B-ionone	Lamongrass

Table 2: Some examples of plants used for production of total, or purified standardised extracts for modern therapeutic usage

Plant	Standard Extract
Aloe spp.	Extract containing 20% hydroxy-anthracenes calculated as Aloin.
Atropa belladonna	Extract containing 1% alkaloids calculated as hyoscyamine.
Cassia angustifolia	Extract containing 45% sennosides calculated as sennoside B.
Capsicum annum	Oleoresin containing 8-10% capsaicin.
Centella asiatica	Extract containing 70% triterpenic acid.
Cephaelis ipecacuanha	Extract containing 6% alkaloids calculated as emetine.
Commiphora mukul resin	Standardised ethyl acetate extract containing 5-7% guggulsterones.
Digitalis spp.	Digitalis total extract
Glycyrrhiza glabra	Liquorice extract, total or purified.
Hyocyamus niger	Extract containing 1% alkaloids determined as Hyoscyamine.
Panax ginseng	Extract containing 10% saponins calculated as ginsenoside Rg 1
Valeriana officianalis & Valeriana wallichi	Extract containing 1.3% and 0.75% Valtpoate
Zingiber officinalis	Total extract/oleoresin

SUMMARY

1. IMPORTANCE OF MEDICINAL PLANTS DERIVED THERAPEUTIC AGENTS

Medicinal Plants continue to be of much interest in India as in many other countries, as: (a) traditional systems of medicine continue to be widely practised; it is estimated that 50 to 75% of the population use the drugs of these systems, some because of the lack of easy access to drugs of the modern system, but many by deliberate choice on account of their faith in them; and these drugs are derived mainly from medicinal plants; (b) plant-derived drugs form an important segment of themodern pharmacopoeia and since commercially viable synthetic methods are not likely to become available for many of these drugs there is continuing need for these plants; (c) the source of a number of recently introduced drugs providing major therapeutic gains are plants; this has renewed interest in plants particularly to uncover remedies for diseases for which modern drugs are inadequate and there is presumptive evidence of efficacy in traditional drugs; (d) some important modern drugs are obtained from chemical intermediates obtained from plants; (e) plants are a renewable resource.

In view of this wide-ranging importance of medicinal plants an integrated developmental approach is required to fully exploit the potential of this resource in medicare programmes and to provide this sector a proper scientific economic and industrial base.

2. PRESENT STATUS

a) The Phytochemical Industry: Starting with the making of crude extracts, and tinctures the phytochemical industry has developed into a high-tech industry for manufacturing bulk drugs [such as quinine, quinidine, podophyllotoxin, xanthotoxin, vinblastine and senna glycosides] and chemical intermediates from which by chemical and/or enzymatic processes some important drugs [such as etoposide, corticoids hormonal steroids] are made. The phytochemical industry forms an important segment of the bulk drug industry and most of the plants derived bulk drugs are now made locally in India, and some are also exported.

b) Use of Traditional Systems medicines in National Health Programme: In view of the continued and widespread use of drugs of traditional medical system in the country [peoples have faith and relatively easy access to them] it has been generally accepted that traditional drugs should also be used along with modern drugs for national medicare services. Although historically the traditional systems drugs were manufactured by individual physicians, now much of the production is carried out by large manufacturing companies with modernised manufacturing practices, dosage forms, packaging and quality control standards. The production of traditional systems drugs by these companies now forms a sizable portion of the total organised pharmaceuticals production in the country [about US $ 650 million production in 1988].

c) Development & Introduction of improved varieties of plants: A number of plants required for production of drugs are indigenous to India, but many exotic species have been successfully introduced; in some plants varietal improvements and agronomical practice modifications have been carried out to increase the yield of active constituents. Tissue culture and recombinant DNA techniques have also been used for development and field introduction of new varieties of medicinal plants.

3. R&D FOR MEDICINAL PLANTS DERIVED THERAPEUTIC AGENTS

In view of the use of medicinal plants both in modern and traditional systems of medicine, each having its own R&D needs and approaches, and the impact that contemporary developments in biotechnology, pharmaceutical sciences, and chemical technology are likely to make on cultivation and processing of medicinal plants, an integrated approach is required for greater utilisation of this important renewable resource. The R&D in this area should emphasise the following:-

a) Process Technology for Industrial Production: A great deal of emphasis has been given to the industrial production of drugs and chemical intermediates obtainable from plants, which has required introduction, latest developments in chemical technology and separation methods for processing of plants and isolation of individual constituents to optimise the yields/recovery and reduced energy and solvent inputs. This requires continuous R&D inputs.

b) Cultivation of Medicinal Plants: The availability of medicinal plants has a critical role on the development of this sector. The R&D in this area should include:-

i) Preservation of existing germ-plasm and practices to protect threatened species
ii) Introduction of new species by conventional or tissue culture techniques
iii) Improvement of existing varieties by conventional methods and/or by new genetic engineering techniques.

c) Discovery of new Drugs:

i) Ethnomedical Leads: The reported or observed biological activity of medicinal plants of traditional systems or ethnomedical sources has been one important source of leads for development of modern drugs. There has, therefore, been a sustained interest in R&D on medicinal plants for the discovery of new drugs. Further, the undercurrent of disenchantment with modern drugs on account of their toxic side-effects has led to a resurgence of interest in natural products and traditional system drugs all over the world. There is, therefore, a sharper focus in R&D on medicinal plants for discovery and/or development of new drugs.

ii) Broad biological screening: A systemic biological screening of local flora, which involves systematised collection of plants their proper identification, preparation of extracts and biological screening, particularly for those conditions for which existing drugs are inadequate for essential component of drug research. Those extracts which show activity are then followed up for chemical characterisation and drug development of fractions and/or pure constituents. This has provided many useful leads, some of which have been used for development of new drugs.

d) Traditional System remedies: To fully exploit the potential of traditional medical system remedies much R&D is needed which should include the following:-

i) Updating the technology for production; simplification and modernisation of production methods; development of quality control standards using modern instrumentation and/or bioassay methods; determination of pharmacokinetic and bio-availability parameters, wherever possible and necessary.

ii) Update/validate the therapeutic results of traditional system drugs using modern methods and tools particularly for conditions such as hepatitis, dementias and degenerative disorders and immunomodulators for which modern drugs are inadequate.

iii) Carry out minimal preclinical toxicology and human safety studies for some important drugs particularly those used for chronic disorders and which would need to be used for long periods.

iv) Determining the place of these remedies in National Health Programmes in the light of contemporary developments in therapeutics.

e) Regional Cooperation: This area of R&D on medicinal plants and industrial production based on them specially lends itself to collaboration among developing countries particularly of a region. The health problems, the socio-cultural background and natural resources are similar, and the experience of one would be more profitably applicable to the other. The collaborative programmes could include one or more of the following areas: survey of a medicinal plant resources; cultivation of medicinal plants including genetic improvement; screening of medicinal plants for development of new drugs; development of technology for production of medicinal plant products; sharing of resources for production based on medicinal plants; establishing joint production plants. It would be useful to set up Regional Medicinal Plant Research Centres to foster and promote regional cooperation in this field.

4. CONCLUSION

A comprehensive and well integrated developmental approach is required for fuller utilisation of the economic and industrial potential offered by medicinal plants, which should include development of a self-reliant technology base for industrial production of medicinal products needed both in modern and traditional pharmacopoeias, cultivation of medicinal plants and R&D for development of new drugs from plants and based on leads provided by traditional medical system remedies.

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